Version of Amended Specification Paragraphs With Markings to Show Changes Made:

NOTE: Insertions are marked by underlining and bold text.

Please replace the last paragraph on page 3 (which wraps around to the top of page 4) with the following paragraph:

Despite their sequence variations, all five subfamilies of the Ras superfamily share conserved structural features. Four conserved sequence regions (motifs I-IV) have been studied in the LMW GTP-binding proteins. Motif I is the most variable but has the conserved sequence, GXXXXGK **(SEQ ID NO:26)**. The lysine residue is essential in interacting with the .beta.- and .gamma.-phosphates of GTP. Motif II, III, and IV contain highly conserved sequences of DTAGQ **(SEQ ID NO:27)**, NKXD **(SEQ ID NO:28)**, and EXSAX **(SEQ ID NO:29)**, respectively. Specifically, Motif II regulates the binding of gamma-phosphate of GTP; Motif III regulates the binding of GTP; and Motif IV regulates the guanine base of GTP. Most of the membrane-bound LMW GTP-binding proteins generally require a carboxy terminal isoprenyl group for membrane association and biological activity. The isoprenyl group is added posttranslationally through recognition of a terminal cysteine residue alone or a terminal cysteine-aliphatic amino acid-aliphatic amino acid-any amino acid (CAAX**; SEQ ID NO:30**) motif. Additional membrane-binding energy is often provided by either internal palmitoylation or a carboxy terminal cluster of basic amino acids. The LMW GTP-binding proteins also have a variable effector region, located between motifs I and II, which is characterized as the interaction site for guanine nucleotide exchange factors (GEFs) or GTPase-activating proteins (GAPs). GEFs induce the release of GDP from the active form of the G protein, whereas GAPs interact with the inactive form by stimulating the GTPase activity of the G protein.

Please replace the last full paragraph on page 4 with the following paragraph:

A number of Rho GTP-binding proteins have been identified in plasma membrane and cytoplasm. These include RhoA, B and C, and D, rhoG, rac 1 and 2, G25K-A and B, and TC10 (Hall, A. et al. (1993) Philos. Trans. R. Soc. Lond. (Biol.) 340:267-271). All Rho proteins have a CAAX **(SEQ ID NO:30)** motif that binds a prenyl group and either a palmitoylation site or a basic amino acid-rich region, suggesting their role in membrane-associated functions. In particular, RhoD is a protein that functions in early endosome motility and distribution by inducing rearrangement of actin cytoskeleton and cell surface (Murphy, C. et al. (1996) Nature 384:427-432). During cell adhesion, the Rho proteins are essential for triggering focal complex assembly and integrin-dependent signal transduction (Hotchin, N. A. and Hall, A. (1995) J. Cell Biol. 131:1857-1865).

Please replace the last paragraph on page 4 (which wraps around to the top of page 5) with the following paragraph:

The Ras subfamily proteins already indicated supra are essential in transducing signals from receptor tyrosine kinases (RTKs) to a series of serine/threonine kinases which control cell growth and differentiation. Mutant Ras proteins, which bind but cannot hydrolyze GTP, are permanently activated and cause continuous cell proliferation or cancer. TC21, a Ras-like protein, is found to be highly expressed in a human teratocarcinoma cell line (Drivas, G. T. et al. (1990) Mol. Cell. Biol. 10: 1793-1798). Rin and Rit are characterized as membrane-binding, Ras-like proteins without the lipid-binding CAAX **(SEQ ID NO:30)** motif and carboxy terminal cysteine (Lee, C.-H. J. et al. (1996) J. Neurosci. 16: 6784-6794). Further, Rin is shown to localize in neurons and have calcium-dependant calmodulin-binding activity.

Remarks/Conclusions

A Notice to Comply mailed June 18, 2003 (a copy of the Notice is submitted herewith) indicated that certain amino acid sequences appearing in the specification are not properly identified by sequence identification numbers. In response, Applicants hereby submit a Third Substitute Sequence Listing (including a paper copy and computer readable form on diskette) along with the above-indicated amendments to the specification.

Respectfully submitted,

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Date: July 18, 2003

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